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EXAMINER	
LEE, BETTY L	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/754,485	HENDERSON, DANIEL R.	
	Examiner	Art Unit	
	Betty Lee, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/15/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *6,7,19-34 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8-18,35 and 37-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed Aug 15, 2005, is acknowledged. New claims 53-56 are added. Claims 1-56 are pending.

Applicant's arguments regarding election of species for a) the ligands pIgR and pIgR stalk, b) the targeting element as antibody, antibody fragment or single-chain variable region fragment c) disease of the airway as COPD, asthma and emphysema were all persuasive. Therefore, the election of species requirement as it pertains to the species listed *supra* is withdrawn.

Applicant's arguments regarding the species election of diseases of the airways were persuasive to the extent that individual species COPD, asthma and emphysema are encompassed by disease of the airways. Applicant's election with traverse of 'polypeptide' for the therapeutic agent is noted. Applicant's arguments have been fully considered and are persuasive in part. Applicant argues that anti-tumor agent, anti-infective agent, anti-angiogenesis agent, apoptosis inducer, immune system modulator, taxol, enzyme, interleukin, interferon, TNF, cytokine, chemokine, an antibody, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12, IL-13, IL-15, interferon-α, interferon-β, interferon-γ, IP-10, I-TAC, MIG and the newly added α1-antitrypsin are all encompassed within 'polypeptide' species. Although, an enzyme, interleukin, interferon, TNF, cytokine, chemokine, an antibody, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12, IL-13, IL-15, interferon-α, interferon-β, interferon-γ, IP-10, I-TAC, MIG and α1-antitrypsin are all polypeptides; an anti-tumor agent anti-infective agent, anti-angiogenesis agent,

apoptosis inducer, immune system modulator and taxol are not necessarily polypeptides. Therefore, the species of enzyme, interleukin, interferon, TNF, cytokine, chemokine, an antibody, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12, IL-13, IL-15, interferon-α, interferon-β, interferon-γ, IP-10, I-TAC, MIG and α1-antitrypsin will be rejoined with the polypeptide; however, the species of anti-tumor agent, anti-infective agent, anti-angiogenesis agent, apoptosis inducer, immune system modulator and taxol are withdrawn from consideration as directed to non elected species.

Applicant's election of SEQ ID NO: 44 as the pIgR amino acid sequence and SEQ ID NO: 37 to the carboxy terminus as the pIgR region with traverse is noted. Applicant argues that the remaining pIgR regions are encompassed by the "R8a" sequence. As the regions listed in the series are part of the region between amino acid 315 and the carboxy terminus of pIgR, the species are rejoined and will be examined together.

Claims 1-5, 8-18, 35, 37-56 are under examination to the extent that they read on the species of pIgR (to include pIgR stalk, SEQ ID NO: 44 and pIgR region "R8a"), antibody (to include antibody fragment or single-chain variable region fragment), disease of the airways (to include COPD, asthma and emphysema), and polypeptide (to include enzyme, interleukin, interferon, TNF, cytokine, chemokine, an antibody, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12, IL-13, IL-15, interferon-α, interferon-β, interferon-γ, IP-10, I-TAC, MIG and α1-antitrypsin).

Claims 6, 7, 19-34 and 36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/15/2005. Claims 1-5, 8-18, 35, 37-56 are under examination.

Claim Objections

1. Claims 2, 5, 8, 9, 10, 18, 42 and 43 are objected to as containing non-elected subject matter. The claims encompass nonelected species.

2. Claim 9 is objected to under 37 CFR 1.75(c) as being in improper form because the claim is dependent on a non-elected claim 8. Correction is required.

Claim 56 is objected to under 37 CFR 1.75(c) as being in improper form because the claim is dependent on non-elected claim 30.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-5, 8-18,35, 37-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of fusion proteins such as diabody sFv directed to a pIgR epitope, sFv-α IFN, sFv-beta-IFN IL-2-sFv and sFv-I-TAC fusion proteins, does not reasonably provide enablement for treating specific lung diseases such as COPD or emphysema. Neither is the applicant enabled for administration of ANY polypeptide e.g.α-1 antitypsin, as a therapeutic agent to treat or

prevent ALL lung diseases. In addition, the applicant is not enabled for the use of α-1 antitypsin fusion protein to treat emphysema or COPD. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

4. The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a method of treating or preventing a lung disease (or more specifically asthma, COPD or emphysema) in a subject by administering via pulmonary, oropharyngeal or nasopharyngeal route a compound comprising a therapeutic agent (any polypeptide including but not limited to enzyme, interleukin, interferon, TNF, cytokine, chemokine, an antibody, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12, IL-13, IL-15, interferon-α,

interferon-β, interferon-γ, IP-10, I-TAC, MIG and α1-antitrypsin) and a targeting element (antibody) directed to a ligand, wherein the targeting element confers apical to basolateral transcytosis to the therapeutic agent.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that it is impossible to prevent a disease from occurring in any subject. For example, cystic fibrosis, a genetic disease due to a mutation in a cystic fibrosis gene, causes inflammation of the lung. Doull (Arch. Dis. Child, 85:62-66, 2001) teaches that asthma, allergic bronchopulmonary aspergillosis, disseminated bronchietasis and diffuse panbronchiolitis are associated with one or more cystic fibrosis transmembrane conductance regulator (CFTR) mutations (pg 63, Box 1). Doull also teach that bacterial infection of the airway can occur in cystic fibrosis (pg 64, col 1) and that the bacterial pathogens infecting the cystic fibrosis airway change with age (pg 64, col 2). Therefore, the art teaches that lung disease, such as asthma, is a secondary disease associated with a genetic mutation of the cystic fibrosis gene. It would be impossible to use the claimed invention to prevent a genetic defect. Lung cancer is also another example of lung disease that is caused by smoking and/or genetic disposition.

The instant claims additionally lack an enabling disclosure for using any polypeptide to treat lung disease. A polypeptide is a general term referring to any protein. All polypeptides are not therapeutic, e.g. viral and bacterial toxins, cytomegalovirus antigens and listeriolysin are polypeptides, which cannot be used therapeutically. The art teaches (Boer DDT, 10:93-106, 2005) that many cytokines and chemokines are elevated in COPD (pg 95,Table 1) and that chimeric antibodies against

TNFα have adverse side effects in clinical trials, especially reactions around the site of administration, a delayed hypersensitivity-like reaction, new onset of autoimmunity, drug-induced systemic lupus erythrematosis and demyelination, serious infections, vasculitis or malignancies, which leads to loss of efficacy of these polypeptide drugs (pg 97, col 2).

The amount of direction or guidance present and the presence or absence of working examples: There are no working examples directed to administration of polypeptides to treat lung disease e.g. emphysema, COPD or asthma. There are no working examples drawn to using the specific polypeptide α1-antitrypsin to treat emphysema, COPD or asthma in an animal model. There is no support in the specification for the use of α1-antitrypsin for emphysema, COPD or asthma except as a citation (Ferkol *et al.*, Am. J. Resp. Crit. Care Med. 161:944-951, 2000). Ferkol, *et al* teach the use of anti-single chain Fv/α1-antitrypsin in an *in vitro* system (pg 946, col1). Although the fusion protein has been tested in epithelial and MDCK cell system, the art does not recognize this as predictive of in vivo efficacy. The specification discloses rat and monkey studies with pIgR Stalk sFv and the measurement of plasma concentrations of the fusion proteins. However, there is no indication that merely administering the pIgR Stalk Fv to monkeys has any therapeutic effect on any particular disease. Example 16 shows aerosol administration of diabodies of sFv directed to a pIgR epitope. The example compares the serum level of sFv administered by inhalation, instillation and IV and shows that pulmonary delivery of sFv directed to pIgR can provide apical to basolateral transport of agent. The effective transport of agents across

the pulmonary epithelium does not necessarily translate to effective treatment of lung disease. However, there are no examples of polypeptides listed above which show efficacy in animal studies. The specification does not disclose any therapeutic polypeptides e.g. α1-antitrypsin/pIgR fusion protein in an animal model. The specification discloses the construction and expression of sFv-α IFN, sFv-beta-IFN IL-2-sFv and sFv-I-TAC fusion proteins and a transwell trancytosis assay of IL-2-sFv. The examples are not commensurate in scope with the claims, which are directed to *in vivo* therapy.

The breadth of the claims and the quantity of experimentation needed: Given the teachings of unpredictability which are found in the art, detailed teachings are required in the specification to enable the claimed invention. These teachings are absent. There are no teachings sufficient to overcome the degree of unpredictability of using any polypeptide to treat COPD or other lung diseases. Therefore the claims are not enabled for preventing all lung diseases by administering pIgR fusion proteins; for administering any polypeptide as a therapeutic agent to treat lung disease; or for the use of α1-antitrypsin as a therapeutic agent fused to sFv to treat specific lung diseases, such as emphysema, asthma and COPD. It would require an undue amount of experimentation by one of skill in the art to practice the invention commensurate in scope with the claims, given the lack of guidance in the specification.

5. Claims 9, 10 and 53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The therapeutic agent, α1-antitrypsin is considered new matter because there is no support for the proposed use of α1-antitrypsin as a therapeutic agent in the specification. There is no conception in the specification as originally filed of using α1-antitrypsin in the claimed method. The only mention of α1-antitrypsin is in reference to a citation by Ferkol, *et al.* who teach the administration of a fusion protein consisting of α1-antitrypsin linked to single-chain Fv directed against the secretory component of the human pIgR (pg 23, paragraph 0384).

6. Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is *whatever is now claimed* (see page 1117).

A review of the language of the claim indicates that these claims are drawn to a genus, i.e."functional derivatives of any thereof" from the group of therapeutic agents consisting of IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12, IL-13, IL-15, interferon-α, interferon-β, interferon-γ, IP-10, I-TAC, MIG and α1-antitrypsin.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention.

There are a few species of the claimed genus disclosed that are within the scope of the claimed genus, *i.e.*IL-2, I-TAC, IFNα and IFNβ. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. There is substantial variability among the species.

One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus of which comprises "functional derivatives of any thereof" from the group of therapeutic agents consisting of IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12, IL-13, IL-15, interferon-α, interferon-β, interferon-γ, IP-10, I-TAC, MIG and α1-antitrypsin. The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

7. Claims 15-17 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A review of the language of the claim indicates that these claims are drawn to a genus, i.e. "therapeutic portion or metabolite thereof" of a compound.

There are a few species of the claimed genus disclosed that are within the scope of the claimed genus of compounds, *i.e.* IL-2, I-TAC, IFNα and IFNβ. The disclosure of even a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. There is substantial variability among the species.One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus of which comprises "therapeutic portion or metabolite thereof" of IL-2, I-TAC, IFNα and IFNβ.

The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 9, 10, 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claimed invention recites the method wherein the therapeutic agent comprises one or more agents or 'functional derivatives of any thereof'. The specification fails to teach the parameters of 'functional derivatives' of a therapeutic

agent such as α1-antitrypsin or any polypeptides. Thus, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

Claims 15-17 recite the compound or 'a therapeutic portion or metabolite thereof' is administered to the subject. However, the specification fails to teach the parameters of 'a therapeutic portion or metabolite thereof'. Thus, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

9. Claims 37 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The first occurrence of an acronym such as 'COPD' in claim 37 should be accompanied by the full name of the disease designated by the abbreviation. Similarly, the first occurrence of acronyms such as PTD and MTS in claim 44 should be accompanied by the full name of the disease designated by the abbreviation.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section

351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 8-18, 35, 37-43, 48-52, 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Houston, *et al* (WO02074787 A2).

The claimed invention is drawn to a method of treating or preventing a lung disease (lung cancer, asthma, emphysema and respiratory infections) in a subject by administering a compound comprising a therapeutic agent (polypeptide, enzyme, interleukin, interferon, TNF, cytokine, chemokine, an antibody, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12, IL-13, IL-15, interferon-α, interferon-β, interferon-γ, IP-10, I-TAC or MIG) and a targeting element (i.e. antibody) directed to a ligand (i.e. pIgR, pIgR stalk, or more specifically the pIgR amino acid sequence of SEQ ID NO: 44 or the region R8a to the carboxy terminus,. SEQ ID NO: 37), wherein the targeting element confers apical to basolateral transcytosis to the therapeutic agent.

Houston, *et al* teach compositions and methods for obtaining targeting elements directed to pIgR that undergoe apical to basolateral (reverse) transcytosis (see abstract). Furthermore, Houston, *et al* teach that polypeptides which may be incorporated into the compositions include cytokines, antibodies, antibody fragments, enzymes, IFNs e.g. IFNα, IFNβ, IFNγ, interleukins (IL-1 to IL-15) and other growth hormones (pg 13, lines 15-20). Houston, *et al* teach that an antibody has two antigen binding domains (pg 52, line 1) which would be binding sites for the ligand (claim 47). Houston *et al* further teach that chimeric pIgR-targeting proteins may be dispersed in dry and liquid formulations, which include lyophilized powders that are well suited for aerosol delivery to the sinuses or lung (pg 60, lines 23-26). In addition, Houston, *et al*

teach that micronized particles e.g. 5-100 μm can be coated with chimeric pIgR-targeting protein (pg 61, lines10-18) and that aerosols, droplets and sprays may range from 1-200 μm in size (pg 62, lines 20-21). Furthermore, Houston, *et al* teach that their method can be used for diseases of the respiratory system, such as lung cancer and tumors, asthma, pathogenic infections and allergy-related disorders (pg 65, lines 23-26). Houston, *et al* teach that the compositions can be formulated as a vaccine with a pharmaceutical carrier (pg 62, lines 6-9, pg 63, lines 32-33, pg 64, lines 1-12). Houston, *et al* teach that derivatives of monoclonal antibodies, like a single-chain Fv antibody fragments can be made to bind to a specific site on pIgR (pg 73, lines7-9) and discloses an antibody, sFV-5A that binds to a known epitope, i.e. QDPRLF (SEQ ID NO: 44) of the instant application (pg 71, lines 27-30). In addition, Houston, *et al* teach the pIgR amino acid sequence of SEQ ID NO: 44 and the region R8a (SEQ ID NO: 37 to the carboxy terminus of pIgR) of the instant application (pg 2/8, Fig 2A, pg 19, lines 32).

11. Claims 1-5, 37, 45 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferkol *et al.* (J. Clin. Invest. 92:2394-2400, 1993).

The claimed invention is drawn to a method of treating or preventing a lung disease (chronic obstructive pulmonary disease or COPD) in a subject by administering via the pulmonary, oropharyngeal or nasopharyngeal route a compound comprising a therapeutic agent and a targeting element directed to a ligand, wherein the targeting element confers apical to basolateral transcytosis to the therapeutic agent. Claims 45 and 46 are drawn to a second targeting element e.g. antibody.

Ferkol *et al* teach that cystic fibrosis is a chronic obstructive pulmonary disease (pg 2394, col 2). Ferkol *et al.* teach construction of the Fab fragment of anti-pIgR antibody covalently linked to poly (L-lysine) as the linker (pg 2395, col 1). Ferkol *et al.* teach that targeting pIgR may be a method of introducing normal copies of cystic fibrosis transmembrane conductance regulator (CFTR) gene into respiratory cells in patients with cystic fibrosis (pg 2399, col 1). Ferkol *et al* teach administration of an anti-pIgR antibody to deliver a therapeutic agent, e.g. copies of CFTR gene to patients with a lung disease. Ferkol *et al.* teach the administration of dimeric IgA as a second targeting element (pg 2397, col 1 and 2). The second targeting agent is also an antibody and therefore is substantially identical to the first targeting agent as they are both antibodies.

12. Claims 1-5, 11, 12, 18, 37, 39, 42, 47-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Mostov *et al.* (WO0172846 A2).

The claimed invention is drawn to a method of treating or preventing a lung disease (COPD) in a subject by administering via inhalation in the pulmonary, oropharyngeal or nasopharyngeal route a compound comprising of a therapeutic agent (polypeptide) and a targeting element (antibody) directed to a ligand (pIgR), wherein the targeting element confers apical to basolateral transcytosis to the therapeutic agent. . Claims 11 and 12 are further drawn to. The claims are further drawn to administration of liquid and solid particles and to the targeting element comprising two to four single chain

variable fragments (sFv), where one or more is covalently or noncovalently linked to the therapeutic agent and at least one sFV binds to a non-secretory component of pIgR.

Mostov, *et al.* teach a method of transcytosing a ligand from the apical to a basolateral side of a cell of an organ in an animal, by binding the ligand to a region of the pIgR (pg 8, lines 15-20). Mostov, *et al.* teach that the ligand may have a binding component for a region of pIgR and a biologically active component (pg 10, lines 13-19) and that the ligand (humanized antibody, scFv) can bind to an epitope of pIgR which is identical to SEQ ID NO: 44 of the instant application (pg 10, lines 1-10, SEQ ID NO: 10, pg 50, lines 32-33, pg 3/5, Fig 3). Mostov, *et al.* teach that "binding of therapeutic ligands to pIgR has utitlity in extending the duration of the ligands in the lumen of various passageways and increasing their effectiveness" (pg 15, lines 4-6). Furthermore, Mostov *et al* teach delivery of agents to the nose or sinuses by nose drops or sprays and to the lung by inhalation of aerosolized mists or finely dispersible dry powders (pg 15, lines 15-17). Mostov *et al.* teach that single chain Fv portion of an antibody or disulfide stabilized Fv antibody can be used (pg 49, lines 4-23). Mostov *et al.* teach the protein-Fab complex coupled to adenovirus (pg 65, lines 29-30).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9-12, 53, 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis, *et al* (US Patent 6072041) in view of Mostov *et al.* (WO0172846 A2).

The claimed invention is drawn to a method of treating or preventing a lung disease in a subject by administering a compound comprising of a therapeutic agent (i.e. α1-antitrypsin, enzyme, interleukin, interferon, TNF, cytokine, chemokine, an antibody, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12, IL-13, IL-15, interferon-α, interferon-β, interferon-γ, IP-10, I-TAC, MIG) and a targeting element (i.e. antibody) directed to a ligand (i.e. pIgR or pIgR stalk), wherein the targeting element confers apical to basolateral transcytosis to the therapeutic agent.

Davis, *et al* teach the construction of an anti-human secretory component (SC)/ α1-antitrypsin fusion protein in prokaryotic and eukaryotic cells (col 11, lines 15-59, col 12, lines 24-67). Davis, *et al* teach that it is possible to couple Colistin, an agent used to treat pulmonary infections in patients with cystic fibrosis, to the anti-human SC Fv antibody (col 5, lines 61-63). In addition, Davis, *et al* teach that other proteins which may be used as therapeutic components include cytokines, IL-2, IL-10 and peptide antibodies and that the fusion protein may comprise other amino acid sequences, in addition to the single chain antibody and the therapeutic protein (col 6, lines 47-52). However, since their fusion protein is targeted to the SC portion of pIgR, the protein is transcytosed from the basolateral to the apical side of the cell. Davis, *et al* do not teach the apical to basolateral transcytosis of their fusion protein.

Mostov *et al.* teach a method of transcytosing a ligand with a biologically active component (pg 10, lines 13-19) from the apical to a basolateral side of a cell of an organ in an animal, by binding the ligand to a region of the pIgR (pg 8, lines 15-20).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modify a fusion protein with α1-antitrypsin as taught by Davis, *et al* to the pIgR stalk as taught by Mostov, *et al.* The person of ordinary skill in the art would have been motivated to construct the fusion protein with α1-antitrypsin in order to deliver the therapeutic agent via aerosol to inhibit inflammation at the surface and have the fusion protein deliver it from the apical to the basolateral direction in the pulmonary epithelial cells of the lung to transfer therapeutic proteins like α1-antitrypsin by receptor-mediated endocytosis.

Claims 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davis, *et al* (US Patent 6072041) in view of Mostov *et al.* (WO0172846 A2) and further in view of Schwarze, *et al* (Trends Cell Biol. 10(7): 290-5, 2000).

The claimed invention is drawn to a method of treating or preventing a lung disease in a subject by administering via a pulmonary, oropharyngeal or nasopharyngeal route a compound comprising a therapeutic agent and a targeting element directed to a ligand wherein the targeting element confers apical to basolateral transcytosis and wherein the compound further comprises a protein transduction domain (PTD) or membrane transport signal (MTS).

As set forth *supra*, Davis, *et al* teach the construction of an anti-human secretory component (SC)/ α1-antitrypsin fusion protein in prokaryotic and eukaryotic cells and Mostov *et al* teach a method of transcytosing a ligand with a biologically active component from the apical to a basolateral side of a cell of an organ in an animal, by binding the ligand to a region of the pIgR. Neither Davis nor Mostov teach the use of PTD.

Schwarze, *et al* teach that drugs that are larger than bioavailability restriction limit of 600 Da can be synthesized with PTDs to bypass size, charge and polarity constraints (pg 291, col 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a fusion protein comprising the PTD as taught by Schwarze, *et al.* The person of ordinary skill in the art would have been motivated to modify the teachings of Davis, *et al* in view of Mostov, *et al* to deliver the therapeutic agent via aerosol to inhibit inflammation at the surface and have the fusion protein deliver it from the apical to the basolateral direction in the pulmonary epithelial cells via receptor mediated endocytosis. In addition, the person of ordinary skill in the art would have been motivated to construct the fusion protein with PTD because Schwarze, *et al* teach that fusion proteins comprising PTDs peptides are able to confer membrane permeability to proteins that would otherwise not enter cells by cloning them together as a fusion construct.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Betty Lee, Ph.D. whose telephone number is (571) 272-8152. The examiner can normally be reached on M-F 9 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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